

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Adherence to the drugs	Yeaw, 2009 ⁴¹⁸	To assess variations in adherence and persistence for anti-muscarinic medications (overactive bladder)	7,722	78.20%	NR	Retrospective analysis	1 year	PharMetrics Patient-Centric Database, a nationally representative database of more than 64 million individual members enrolled in 100 U.S. health plans. Patients were included in the analysis if they initiated a retail or mail-order prescription drug of interest between January 1 and December 31, 2005.	At 6 months post-index, with the application of a 60-day refill grace period, persistence rate (A patient was considered persistent until an excessive gap in days supplied occurred; refill gaps of 30, 60, and 90 days were used to calculate persistence for all cohorts) for OAB medications was 28% and at 1-year it was 18%. Mean (SD) patient adherence calculated as a continuation measure of PDC over a 12-month followup period was 35% (32%) for OAB medications.
Drug fesoterodine	Michel, 2008 ⁴¹⁹	To review the preclinical and clinical data on fesoterodine	NR	NR	NR	2, 4, 8, or 12mg/day of fesoterodine	NA	20 phase I, three phase II and two phase III studies	4 and 8mg once daily doses were consistently superior to placebo in improving the symptoms of overactive bladder syndrome, with 8mg/day having significantly greater effects than 4mg/day

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Drug fesoterodine	Cole, 2004 ⁴²⁰	NR	728	NR	NR	4, 8 and 12mg fesoterodine once daily	12 weeks	Phase II clinical trial in 728 patients with OAB at sites in Europe, Israel and South Africa	Dropout rates due to adverse events were 4% in the placebo group, 6%, 2% and 12% in the 4mg, 8mg and 12mg groups, respectively. Dry mouth was reported in 9%, 25%, 26% and 34% of patients in placebo and fesoterodine 4-, 8-, and 12-mg groups, respectively
Drug fesoterodine	Kelleher, 2008 ⁴²¹	To present an overview of the components and construction of an economic model using the costs and outcomes associated with fesoterodine	NR	NR	NR	Fesoterodine 4mg daily and fesoterodine 8mg daily	12 weeks	NR	The QALS (Quality-adjusted life year) gained were 0.0111 for tolterodine 4mg/d, 0.0115 for solifenacin, 0.0124 for fesoterodine 4mg/d and 0.0143 for fesoterodine 8mg/d. Fesoterodine may result in fewer overall costs and greater QALYs gained than treatment with tolterodine and solifenacin for the management of patients with OAB and incontinence

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Drug tolterodine	Kelleher, 2002 ⁴²²	To evaluate the long-term effects of tolterodine on the health-related quality of life (HRQoL) of patients diagnosed with overactive bladder with incontinence	1077	82.00%	NR	Tolterodine 4mg once daily	12 weeks of RCT followed by 12 months of open - label	Participants of 12 weeks RCT continued a one-year open-label, uncontrolled, nonrandomized study at 138 research centers and clinics. They were eligible if they had an average of 8 or more micturitions per 24 hours over a 7-day period and at least 5 urge incontinence episodes per week	Mean changes in the KHQ scores from rollover (start of open-label study) and month 12: in PT (placebo-treated group: incontinence impact=-12.7 (1.8) and in TT (tolterodine-treated) group=-5.9 (1.2); role limitations in PT=-11.6 (1.8) and in TT=-4.1 (1.2); physical limitations in PT=-10.1 (1.7) and in TT=-2.9 (1.2) severity (coping) measures in PT=-5.1 (1.3) and in TT= -2.1 (0.9) and symptom severity in PT=-6.6 (0.9) and in TT=-0.8 (0.6)

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Drug tolterodine	Siami, 2002 ⁴²³	To assess the speed of onset of therapeutic benefit with tolterodine extended-release 4mg	1138	73.46%	NR	Tolterodine extended-release 4mg once daily	12 weeks	The Speed of Onset of Therapeutic Assessment Trial (STAT). Men and women aged ≥18 years with a diagnosis of OAB, with symptoms of urinary frequency (≥8 micturitions/24 hours) and urgency with or without urge incontinence. Patients were categorized into drug-naïve and previously treated (that is those receiving pharmacologic treatment other than tolterodine for OAB)	72% of the maximum effect on urge incontinence was observed in both groups; and 84.7% of drug-naïve patients and 83.6% of previously treated patients perceived a benefit from benefit. Dry mouth was reported in 15.5% of drug naïve patients and 15.5% of previously treated patients also. In drug - naïve group:10.8% had mild dry mouth, 3.1% had moderate and 1.6% had severe and in previously treated patients 11.85 had mild dry mouth, 3% had moderate and 0.7% had severe dry mouth

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Drug tolterodine	Kreder, 2002 ⁴²⁴	To examine the long-term safety, tolerability and efficacy of tolterodine extended-release in patients who had completed 12 weeks of treatment in a randomized, double-blind study comparing tolterodine ER4mg once daily, tolterodine immediate-release 2mg twice daily and placebo	1077	82%	NR	Tolterodine extended-release 4mg once daily	12 month open-label after 12 weeks RCT	Men and women aged ≥18 years with urinary frequency (≥8 micturitions/24 hours; urge incontinence (≥5 incontinence episodes per week) and urgency; and symptoms of overactive bladder for ≥6 months	A total of 75% of patients had an improvement in their bladder condition and 51% had an improvement in their urgency. 139 (12.9%) reported dry mouth, 35 (3.3%) had constipation, 24 (2.2%) had dyspepsia, 43 (4%) had upper respiratory tract infection, 28 (2.6%) had bronchitis, 44 (4.1%) had UTI, 23 (2.1%) had cystitis, 26 (2.4%) had headache
Duloxetine	Wernick, 2007 ⁴²⁵	The cardiovascular safety profile of the SNRI duloxetine through evaluation of cardiovascular-related parameters and adverse events	Data from 42 placebo-controlled clinical trials of 8,504 patients			Duloxetine 40-80mg vs. placebo	Varied	Adults with major depressive disorder (15 studies), diabetic peripheral neuropathic pain (3 studies), fibromyalgia (2 studies), generalized anxiety disorder (3 studies) and lower urinary tract disorders (19 studies, all related to incontinence).	Duloxetine resulted in decrease from baseline in RR, QRS and QT intervals but not clinically significant

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Duloxetine	Michel, 2009 ⁴²⁶	To evaluate the safety and tolerability of duloxetine in the treatment of female stress incontinence in women greater than 18 years of age	5879	100	100	20mg duloxetine daily	Not reported	Female patients with stress incontinence and greater than 18 years of age	Adverse events occurred at a rate of 9.1% in the duloxetine group and 5.7% in the control group
Estrogen combined with tolterodine	Serati, 2009 ⁴²⁷	To compare the efficacy of antimuscarinic alone versus antimuscarinic combination with local estrogens for OAB; to verify whether risk factors for lower antimuscarinic efficacy can be overcome by the concomitant use of local estrogens	236	100	Not reported	Subjects in group 1 were prescribed only tolterodine ER 4mg once daily to be taken at night for at least 12 weeks; subjects in group 2 were prescribed both tolterodine ER 4mg and concomitant estrogen cream application once daily to be taken at night for at least 12 weeks	12 weeks	Postmenopausal (women were considered postmenopausal if they were >40 years old and reported absence of menses for at least 12 months) women with symptomatic urodynamically proven detrusor overactivity	The efficacy of the therapy was 80.6% in the tolterodine group and 82% in the tolterodine and estrogen group. 62.8% were cured, 17.8% showed improvement, and 19.4% were nonresponders in the tolterodine alone; and 62% were cured, 20% showed improvement, and 18% were nonresponders in the tolterodine and estrogen group
Antimuscarinic drugs and bladder training vs. bladder training alone	Ghei, 2006 ⁴²⁸	Cooperative effectiveness of antimuscarinic drugs and bladder training vs. bladder training alone in adults with urge UI	664 women and 44 men	93.8	100	Oxybutynin, tolterodine, or imipramine combined with antimuscarinic drugs and bladder	16 weeks	Adults with mean 54 years and overactive bladder and no significant stress UI	Antimuscarinic drugs were more effective reducing UI

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Solifenacin VOLT (VESIcare Open-Label Trial)	Garely, 2006 ⁴²⁹	VOLT study: perceptions of improvements in symptom bother and health-related quality of life with solifenacin succinate 5- and 10-rag treatments in patients with OAB	2,225	82.2	100	Solifenacin succinate 5- and 10-rag	12 weeks	VOLT (VESIcare Open-Label Trial):adult (aged >18 years) men and women (82.2%) with OAB (urgency, urge UI, frequency, and/or nocturia for ≥3 months)	Some improvement-73%;improvement in UI-60%; Treatment-emergent adverse events -59%; 10% discontinued treatment due to adverse events
Solifenacin VOLT (VESIcare Open-Label Trial)	Garely, 2006 ⁴²⁹	VOLT study: OAB patients' perceptions of improvements in symptom bother and quality of life after solifenacin under conditions reflecting day- to-day practice.	582	92.1	100	Flexibly dosed, once-daily solifenacin	12 weeks	VOLT (VESIcare Open-Label Trial): Adults who had OAB symptoms and urge UI for 3 months or longer	80% of patients achieved improvement in their PPBC score. (61.3%) experienced an adverse event during treatment. Adverse Event: Dry mouth 104 (17.9)
Solifenacin VOLT (VESIcare Open-Label Trial)	Capo, 2008 ⁴³⁰	To report patient satisfaction with treatment, as measured by symptom bother and HRQoL, in a subgroup of Hispanics participating in an open-label study of solifenacin succinate	94	74	63	Solifenacin 5m/d with a dosing option of 5 or 10mg/d at weeks 4 and 8	12 weeks	This is a subset analyses of Hispanic patients enrolled in the VOLT study. Ambulatory men and women 18 years of age and older with symptoms of OAB for at least 3 months and able to use the toilet without difficulty	Over 72% of patients experienced PPBC score improvement. Hispanics receiving solifenacin for OAB reported improvement from baseline in symptom bother and HTQoL

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Solifenacin VOLT (VESIcare Open-Label Trial)	Sand, 2009 ⁴³¹	To determine the efficacy of solifenacin to improve subjects' MBS (Most Bothersome Symptom) based on PRO (Patient-Reported-Outcome) measures	2225	74.56%	26.16%	Solifenacin 5m/d with a dosing option of 5 or 10mg/d at weeks 4 and 8	12 weeks	VOLT is a study in adults with OAB symptoms for >=3 months	The UUI group showed the largest VAS(Visual Analogue Scale), OAB-q, and PPBC improvements. 90.7% of patients whose MBS was UUI showed improved VAS score; 94% of patients whose MBS was UUI showed improved VAS:UUI score; 88.8% of patients whose MBS was UUI showed improved VAS: daytime urinary frequency, and 86.6% of patients whose MBS was UUI showed improvement in VAS: Nocturia score

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Solifenacin VOLT (VESIcare Open-Label Trial)	Mallett, 2007 ⁴³²	To present patient-reported outcomes, as measured by symptom bother and HRQoL, in black patients participating in an open-label study of solifenacin succinate	274 black and 2205 white patients	81.73%	26.83%	Solifenacin 5mg or 10mg once daily according to an individualized flexible-dosing regimen	12 weeks	VOLT study: Men and women aged 18 years or older with symptoms of OAB for 3 months or longer; ambulatory who were able to use the toilet without difficulty and who had not received solifenacin	86.5% of black patients with urinary urgency found it bothersome after solifenacin treatment than at baseline; 87.9% found urge incontinence less bothersome. 46.4% of black subjects experienced an adverse event ; of these 30.1% had at least one treatment-related adverse event; 13% had dry mouth, 6.9% had constipation, 2.5% had blurred vision, 2.5% had nausea, and 2.2% had rash. A total of 7.6% black subjects discontinued treatment due to an adverse event.

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Solifenacin VERSUS study	Chancellor, 2008 ⁴³³	To assess the efficacy, tolerability, and effects on HRQL of solifenacin in patients with residual urgency after ≥4 weeks of treatment with tolterodine extended release 4mg	441	88.2	69.39%	Solifenacin 5m/d with dose adjustment at weeks 4 and 8	12 weeks	VERSUS study: patients ages >18 years who had symptoms of OAB for ≥3 months, had been treated with tolterodine ER 4mg for ≥4 weeks and wished to switch therapy because of a lack of sufficient subjective improvement in urgency.	A mean decrease of 3.4 urgency episodes/24 hours (95% CI, -3.8 to -3.0; p<0.001); a mean improvement of 1.2 points (95% CI, -1.3 to -1.1; p<0.001) in PPBC score; changes in all OAB-q scales and domains (symptom bother, coping, concern, sleep, social interaction, and total HRQL) were also statistically significant (p<0.0001). Treatment emergent AEs such as dry mouth (77[17.5%]), constipation (51[11.6%]), and blurred vision (10[2.3%]).

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Solifenacin VERSUS study	Swift, 2009 ⁴³⁴	To evaluate the effects of solifenacin in OAB patients with high symptom bother, this post hoc analysis focuses on the VERSUS 'severe cohort', as defined by patients with scores ≥ 5 on the PPBC scale at baseline (on tolterodine ER mg/d) who remained severe at post-washout (when the patients were receiving no drug)	440, but 116 were from the severe cohort	88.8	Not reported	Solifenacin 5mg/d with dose adjustment at weeks 4 and 8	12 weeks	VERSUS study: Men and women ages >18 years with symptoms of OAB for ≥ 3 months who were ambulatory and able to use the toilet without difficulty and who had received tolterodine ER 4mg/d for ≥ 4 weeks but wished to switch therapy because of lack of sufficient subjective improvement in urgency	In the severe OAB cohort, the mean number of urgency episodes/24 hours decreased by 3.95(97% CI: -4.81, -3.08; $p < 0.0001$)
Solifenacin VERSUS study	Zinner, 2009 ⁴³⁵	To assess changes in health-related quality of life, medical care resource utilization, work, and activity impairment, and health utility among elderly patients with OAB who continued to have urgency symptoms with	441	88	Not reported	Solifenacin 5mg/d with dosing adjustments allowed at week 4 (to 10mg/d) and at week 8 (back to 5mg/d for patients whose dose was increased to 10mg/d at week 4)	12 weeks	Patients who have been treated with tolterodine 4mg/d for ≥ 4 weeks immediately preceding study entry without sufficient improvement in urgency episodes	Subgroup analysis included 108 patients 65 to 74 years of age and 86 patients ≥ 75 years of age. Patients in both groups experienced significant improvement in HRQoL ($p < 0.001$), as well as significant reduction in non protocol-related office visits ($p < 0.001$) and activity management ($p < 0.025$). A significant reduction in the use of

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		tolterodine and were willing to try solifenacin							pads/diapers was reported for patients 65 to 74 years of age ($p < 0.018$), and patients in this age group who were working reported significantly less impairment related to OAB while working during solifenacin treatment than during tolterodine treatment ($p < 0.042$). No significant differences in HUI2/3 scores were observed in either of the elderly groups. Solifenacin was found to improve symptom bother, HRQoL, work productivity, activity participation, and reduced medical care resource utilization in the elderly subjects with OAB who continued to have urgency symptoms with tolterodine and were willing to try solifenacin

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Solifenacin VERSUS study	Zinner, 2008 ⁴³⁶	To evaluate the health outcomes, in terms of medical resource use, work and activity impairment, and health utility, of these patients	441	88.2	Not reported	Solifenacin 5m/day with dose adjustment at weeks 4 and 8	12 weeks	Men and women aged >=18 years with symptoms of OAB for >=3 months who were ambulatory and bale to use the toilet without difficulty and who had been treated with tolterodine ER 4mg/d for at least 4 weeks immediately preceding study entry, but failed to achieve satisfactory improvement in urgency episodes	3.9% discontinued treatment due to adverse events. Patients who were working reported a reduction in percent of work time missed (0.2% vs. 2.1%; p=0.0017), a reduction in percent of impairment while working (11.3% vs. 22.9%; p<0.0001), and a reduction in percent of overall work impairment (11.9% vs. 24.0%; p<0.0001), while a larger group of patients reported a reduction in percent of activity impairment (18.4% vs. 31.6%; p<0.0001)
Treatments for overactive bladder	Sexton, 2009 ⁴³⁷	To assess the impact of OAB on work productivity among employed men and women under the age 65 in the United States	5696	52.92%	7.86%	OAB	NA	Cross-sectional survey of working (full-or part-time) men and women aged 40 to 65 years. This study is part of a study conducted in the US, UK and Sweden. This study focused only on US participants.	Work limitations questionnaire total score, mean (SD): men and continent OAB group=9.3 (14.3) and women and continent group=10.8 (15.6); men and incontinent group=12.5 (16.7) and women and incontinent group=12.6 (16.7); men and no/minimal symptoms=0.6 (4.2) and women and no/minimal

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									symptoms=1.0 (5.3) The regression coefficient in men: urgency with fear of leaking vs. urinary - specific work impairment scores (higher scores indicate greater impairment)=2.232 and in women=0.960; UUI and urinary- specific work impairment scores in men=0.832 and in women=0.941; SUI and urinary-specific impairment scores in men=1.189 and in women=1.312 and nocturnal enuresis and urinary-specific impairment scores in men=1.318 and in women=1.025

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Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Treatments for overactive bladder	Irwin, 2006 ⁴³⁸	To determine the impact of overactive bladder symptoms on issues related to employment, social interactions, and emotional well-being in a population aged 40-64 years	1272	50.80%	NR	OAB	NA	Cross-sectional survey of 11,521 individuals aged 40-64 years and 1,272 of them had OAB	Of those with OAB, approx. 32% reported that having these symptoms made them feel depressed and 28% reported feeling very stressed. 36.4% of OAB with incontinence patients reported emotional stress as compared to 19.6% of patients with OAB and no incontinence. 39.8% of OAB with incontinence patients reported depression as compared to 23.3% patients with OAB and no incontinence. Overall, 76% of individuals reporting OAB symptoms stated that this condition interfered with or made it more difficult to perform daily activities
Treatments for overactive bladder	Wu, 2005 ⁴³⁹	To assess the indirect work loss costs to employers as the result of employees with overactive bladder	21,087	NR	NR	OAB	NA	There were two samples: Sample1 was used to analyze OAB employees' work loss patterns and costs and sample2 was used to assess OAB employees' time	Employees with OAB had 2.2 excess days of work loss absenteeism to medically related absenteeism and 3.4 excess days attributable to disability compared with control subjects (p<0.01 for both comparisons).Multivariate regression analysis revealed that

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								to disability and related risk factors. Individual enrollees in both samples were active employees, 18 to 64 years, with at least one diagnostic code to identify OAB	employees with AOB had 4.4 more days of work loss per year than control subjects (p<0.05). The average annual indirect work loss cost of an employee with OAB was \$1220 from an employer's prospective, which was 1.7 times the indirect work loss cost of a control employee (i.e., \$715) (p<0.01). Multivariate regression analysis showed that OAB imposes an indirect work loss cost burden of \$391 per OAB employee per year from an employers' perspective (p<0.05). Kaplan - Meier analysis showed that employees with OAB had significantly shorter times to disability than did their non-OAB controls
Treatments for overactive bladder	Pelletier, 2009 ⁴⁴⁰	To evaluate adherence with overactive bladder pharmacotherapy and compare costs between patients receiving pharmacotherapy versus	86,734	78%	NR	OAB therapy	1 year	Anonymous, patient-level data were obtained from the PharMetrics Patient-Centric Database (Watertown, MA) which contains	14.4% of the aggregate OAB therapy cohort (43, 576) reached a PDC (proportion of days covered) of 80% or higher, with an average PDC of 32.4%. Following pharmacotherapy

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		nonpharmacological management						adjudicated medical and pharmaceutical claims for more than 90 US managed health care plans across the United States. Patients were 18 years or older and had at least 1 OAB diagnostic code or at least 1 prescription for an antimuscarinic OAB medication during a 24-month index window from January 1, 2005 through December 31, 2006. Subjects were required to have continuous health plan enrollment for a minimum of 6 months before and 12 months after the index date; during periods of continuous enrollment, all medical (inpatient and	initiation, OAB therapy subjects had significantly higher mean (median) total costs compared with nonpharmacological managed subjects (\$9917 [\$4598] vs. \$9657 [\$4299]; p<0.001). Nonpharmacologically managed subjects averaged \$277 for OAB-related outpatient services compared with \$176 for OAB therapy subjects (p<0.001), with 69% more OAB-related physician office visits and more than double the number of OAB-related laboratory tests among nonpharmacologically managed subjects contributing to this difference

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								outpatient) and pharmacy (retail and mail order) claims are captured.	
Treatments for overactive bladder	Schabert, 2009 ⁴⁴¹	To describe the challenges to improving management of overactive bladder outcomes and summarize research findings on critical success factors for supporting OAB treatment	5392	NR	NR	OAB therapy	NA	OAB Persistence Survey: respondents who had been prescribed one antimuscarinic or more for OAB over the prior 12 months	24.5% reported discontinuing one antimuscarinic prescription medication or more during the prior 12 months. Among these patients discontinuing medications, 45.4% reported unmet treatment expectations as the reason for discontinuation

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Treatments for overactive bladder	Bolge, 2006 ⁴⁴²	To examine the impact of overactive bladder on health care resource utilization, daily activities, work productivity, and health complications	441	76.40%	76.40%	Presence of OAB	NA	US National Health and Wellness Survey, 18, and internet population-based survey conducted annually by Consumer Health Sciences. It was administered to a representative sample of registered adult panelists aged 18 years or older in the United States. There were 2602 respondents who reported a history of OAB diagnosed by a physician and out of these 441 respondents were administered the survey for the study.	Of the 196 patients receiving prescription medication, 147 (75%) reported satisfaction with therapy. Of the 31 patients receiving behavioral therapy, 21 (67.7%) were satisfied with treatment. 63 of (48.8%) the 129 respondents taking Kegel exercises were satisfied with this treatment. Impairment in productivity was primarily attributed to lack of concentration (40%), followed by inability to complete tasks (5.4%). OAB reduced their daily activities but 27.6%. Successful treatment of OAB was associated with a significantly lower incidence of complications than unsuccessful treatment(p <0.05)

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Treatments for overactive bladder	Dmochowski, 2007 ⁴⁴³	To examine the effects of OAB on participants; treatment-seeking behaviors, patient satisfaction with oral OAB therapies, and desirable characteristics of new treatments	1228	100%	43%	Cross-sectional survey	NA	Women with symptoms of OAB , aged 40-65 years	87% of current users of OAB medications took their medication daily, with 70% taking it once daily. Only 32% were completely satisfied with their medications. Among respondents with OAB symptoms, 61% felt that less frequent dosing was 'very important' or 'extremely important. Among lapsed users of OAB medications, as compared with current users, significantly higher percentages indicated that it was extremely or very important to not feel nausea (79% vs. 59%), not have dry eyes (68% vs. 54%), not experience constipation as often(71% vs. 59%) and not have to take a high dose of medication (75% vs. 64%)

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Treatments for overactive bladder	Zhou, 2001 ⁴⁴⁴	To identify components of costs attributable to OAB, using medical claims data on insured patients with OAB between 18 and 64 years of age; to examine the demographic and health risk characteristics of patients with a primary or secondary diagnosis of OAB; and to suggest cost-effective treatment strategies for OAB	148,697	NR	NR	Presence of OAB	NA	Two cohorts were identified on the basis of whether individuals had received formal OAB treatment based on the ICD-9 codes for bladder disorders in the claims data. The OAB cohort consisted of 2385 persons with an outpatient claim, primary or secondary ICD-0 code specified for OAB; or persons with an inpatient claim, primary ICD-9 code specified for OAB. The non-OAB cohort included 146,312 patients whose claims over the entire period showed none of the specified ICD-9 codes for OAB	The probability of hospital admission during the year was 20.65 among OAB patients compared with 7% among non-OAB patients. After adjustment for patient risk characteristics, total annual claims for a patient with OAB were 45% higher (p=0.0001), than for a patient without OAB. Annual inpatient claims were 23% higher but not significantly different from claims for a non-OAB patient. Much of the significance in cost for the OAB patients was due to age, sex, and the presence of non-OAB medical conditions.
Treatments for overactive bladder	Brubaker, 2010 ⁴⁴⁵	To identify predictors of self-reported discontinuation of overactive	5392	76%	NR	OAB therapy	1 year	OAB Medication Use Survey. Participants were representatives	Among 2838 respondents at phase3, 1194 had recently discontinued and 1644 were

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		bladder medication using a three-phase survey						of the USA population identified from the Taylor Nelson Sofres (formerly National Family Opinion) household panel	<p>persistent with medications at phase2. Among phase3 respondents who were persistent at phase2, 1040 continued to be persistent at phase3, 280 had discontinued between phases 2 and 3, and 261 had switched medication between phases 2 and 2; 63 had missing prescription at phase 3. Predictors of discontinuing at phase3 included smoking (OR:1.80; 95%CI=1.15-2.83, p=0.010), not knowing whether treating bladder problems requires multiple daily doses of medications (1.71, 1.10-2.67 ;p=0.018), believing (2.11, 1.34-3.33, p=0.001) or not knowing (1.76, 1.23-2.52, p=0.002) whether adverse effects of OAB medications are often severe, and being bothered 'quite a bit or more' by a sudden urge to urinate (1.54, 1.05-2.26; p=0.028). Respondents taking 2 or more medications</p>

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Treatments for overactive bladder	Benner, 2010 ⁴⁴⁶	To evaluate patient-reported reasons for discontinuing antimuscarinic prescription medications for OAB	5392	77.60%	26.80%	OAB therapy	1 year	Representative sample of households in the USA (260,000) that agreed to participate in surveys from the Taylor Nelson Sofres (formerly National Family Opinion)	were less likely to discontinue (OR: 0.45-0.58, p<0.05) Among the 5392 phase2 respondents, 1322 (24.5%) reported discontinuing one or more antimuscarinic prescription AOB medication during the previous 12 months. Most respondents (89%) reported discontinuing OAB medication primarily due to unmet treatment expectations (46.2%) and/or tolerability (21.1%); many respondents in this class switched to a new antimuscarinic agent. A smaller group (11%) indicated a general aversion to taking medication.

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Tolterodine	Coyne, 2008 ⁴⁴⁷	The IMPACT trial: Relationship between treatment-related improvements in overactive bladder (OAB) symptoms as recorded in bladder diaries and patient reported symptom bother, bladder-related problems and health-related quality of life (HRQL).	863	82		Tolterodine ER (4 mg once daily)	12 weeks	>18 years of age (82% women) and have frequency (>8 micturitions per 24 hours) and either urgency (strong, sudden desire to urinate) or urgency urinary incontinence (UUI) (>2 episodes per day as recorded in 3-day bladder diaries)	Tolterodine ER-related improvements in OAB symptoms (assessed by diary variables) and patients' perceptions of changes in symptom bother, bladder-related problems and HRQL (assessed by PPBC and OAB- were significantly correlated).
Tolterodine	Elinoff, 2006 ⁴⁴⁸	The IMPACT trial: the efficacy of tolterodine extended release (ER) for patients' most bothersome overactive bladder (OAB) symptom in a primary care setting	863			Tolterodine ER (4 mg q.d.)	12 weeks	>18 years of age (82% women) and have frequency (>8 micturitions per 24 hours) and either urgency (strong, sudden desire to urinate) or urgency urinary incontinence (UUI) (>2 episodes per day as recorded in 3-day bladder diaries)	Discontinuation due to adverse events-7%; improvement in bladder condition (1 point) - 78.8% and 74.6% of the UUI group; all-cause AE- 51%; treatment-related adverse events -23%

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Tolterodine	Michel, 2007 ⁴⁴⁹	The association between symptoms of UI, bother, and patient satisfaction with treatment using tolterodine in overactive bladder	3,824			Tolterodine ER (4 mg q.d.)	9 months	Adults with OAB	Patient bother was the strongest individual predictor of patient treatment satisfaction in overactive bladder. Changes in episodes of the four symptoms of OAB were not associated with patient satisfaction
Tolterodine	Michel, 2004 ⁴⁵⁰	The impact of concomitant stress incontinence (SI) on the therapeutic effects of tolterodine in patients with OAB with and without concomitant SI.	2,250			2 mg tolterodine twice daily	12 weeks	Adults with OAB	Patients with concomitant III degree SI (but not I or II degree) have significantly less improvement
Tolterodine	Michel, 2002 ⁴⁵¹	The association between patient age and gender and the therapeutic response to tolterodine in adults with OAB	2,251			2 mg tolterodine twice daily	12 weeks	Adults with OAB	Age (OR/yr. 0.978 (0.968–0.987)) and baseline Incontinence (OR 0.744 (0.716–0.774)) was negatively associated with treatment success. Increasing of tolterodine dose was associated with worse response (OR 0.866 (0.784–0.956)) and less tolerance (OR 1.114 (1.028–1.206))

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Tolterodine	Roberts, 2006 ⁴⁵²	The IMPACT trial: the effect of tolterodine extended release (ER) on patient- and clinician-reported outcomes in a primary care setting	863			Tolterodine ER (4 mg once daily)	12 weeks	Adults with overactive bladder (OAB) symptoms for ≥3 months and were at least moderately bothered by their most bothersome symptom	improvement in their overall bladder condition - 79%; Major improvement (improvement of two or more points) - 50.4% and 49.7% of the UUI group
Tolterodine	Sussman, 2007 ⁴⁵³	Timing of the efficacy of tolterodine extended release (ER) in patients with overactive bladder	698			Tolterodine ER (4 mg qd)	12 weeks	Adults (aged ≥18 years) with urinary frequency ≥8 micturitions/24 hours) and urgency (strong and sudden desire to urinate) with or without urgency urinary incontinence (UUI).	Patients with OAB experienced significant reductions in OAB symptoms as early as Day 5 of treatment with tolterodine ER

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Tolterodine vs. Oxybutynin	Lawrence, 2000 ⁴⁵⁴	Adherence to treatment with immediate-release (IR) oxybutynin and Tolterodine`	1531			Tolterodine, IR Oxybutynin	6 months	All patients age 18 years and over who began therapy with either Tolterodine or IR Oxybutynin during April or May 1998	The proportion of patients continuing therapy for 6 months was statistically superior for Tolterodine (32%) Compared with IR Oxybutynin 22% Oxybutynin was switched to another therapy more commonly than Tolterodine (19% and 14%, respectively) Patients discontinuing all therapy within 6 months Men: Tolterodine 33%; Oxybutynin 39 % Women: Tolterodine 67%; Oxybutynin 61% Only 35 (32%) of IR Oxybutynin recipients were fully adherent compared with 87 (53%) of Tolterodine recipients.

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Tolterodine vs. Oxybutynin	Shaya, 2005 ⁴⁵⁵	Predictions of persistence with Tolterodine or Oxybutynin in patients with over active bladder	3,054, 1,637, included in analysis	75		Tolterodine ER, Oxybutynin ER, Oxybutynin 1r 4 weeks		Adults, 75% women, 45% African-American 26% younger than 18, with prescriptions of Tolterodine or Oxybutynin for over active bladder.	Hazard ratio of non persistence adjusted for age, sex, race Oxybutynin 1R vs. Tolterodine ER 30 days 1.09 (0.88; 1.35) >30 days 1.13 (0.84; 1.51) Oxybutynin ER vs. Tolterodine ER <30 days 0.96 (0.6; 1.53) > 30 days 1.47 (1.01; 2.14) Age <18 vs. 18-39 1.56 (1.33; 1.82) > 40 vs. 18-39 0.85 (0.74, 0.97) African Americans vs. Whites 1.22 (1.09; 1.36)
Oxybutynin	Hussain, 1996 ⁴⁵⁶	Effect of oxybutynin on the QTc interval in elderly patients with UI	21		100	Oxybutynin	4 weeks	Elderly	No QTc interval prolongation or ventricular arrhythmias
Oxybutynin	Nilsson, 1997 ⁴⁵⁷	The efficacy and tolerability of controlled release vs. 5-mg conventional oxybutynin twice daily	17	100	100	10-mg Controlled Release Oxybutynin vs. a 5-mg Oxybutynin Tablet	9 weeks	women with urge UI	No difference in efficacy or safety of two formulations

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Oxybutynin	Bemelmans, 2000 ⁴⁵⁸	The efficacy of a low-dose oxybutynin (2.5 mg three times daily) in men and women with symptomatic urge incontinence	416			Oxybutynin (2.5 mg three times daily)	6 weeks	Men and women in primary care practice with symptomatic urge incontinence	Complete symptomatic cure -95%; side effects attributable to the use of oxybutynin - 30%; 10% had to stop the medication because of the severity of these side effects.
Oxybutynin	Radomski, 2004 ⁴⁵⁹	The efficacy of controlled-release (CR) oxybutynin tablet taken once-daily in patients with urinary urge incontinence	12			Oxybutynin (2.5-5 mg bid)	8 weeks	Men and women with urodynamically-confirmed detrusor instability, micturition frequency (≥ 8 voids/day) and/or urinary incontinence (≥ 2 incontinence periods/day)	CR oxybutynin (15 mg OD) was at least as effective as the patients' previous dose of IR oxybutynin (mean dose: 6.7 +/- 2.5 mg/day).

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Oxybutynin	Wang, 2002 ⁴⁶⁰	Risk of ventricular arrhythmia or sudden death after treatment with oxybutynin or other urinary antispasmodics	14,368, 67-75 4% women	70.5		Oxybutynin or flavoxate	Not specified	Adults who filled prescriptions for Oxybutynin or Flavoxate via Medicaid program.	Relative risk of ventricular arrhythmias adjusted for age gender time - varying exposure urinary antispasmodic use 1,23 (0.87-1.75) Concurrent antihistamine/ cytochrome inhibitor use 5.47/1.34- 22.26) Relative risk of sudden death adjusted for age gender, and full of exposure urinary antispasmodic use 0.7 (0.28-1.74) Concurrent antihistamine/ cytochrome inhibitor use 21.5 (5.23-88.32)
Oxybutynin	Diokno, 2002 ⁴⁶¹	Long-term safety of Oxybutynin in adults with over active bladder	904 women and 163 men	84.7	100	Oxybutynin ER	12 weeks-1 year	Adults with urge or mixed UI, mean age 64 years	Discontinuations during 3 month - 25.5%, 1 year-53.8% Discontinuations due to adverse events 15.6% Dry mouth- 5.6% Lack of efficacy -4.9% Central nervous system at 91-180 days Headache-0.6% Dizziness- 0.4% Blurred vision-0.4% Somnolence 0.2% (181 day) Confusion 0.1%

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Oxybutynin MATRIX study	Pizzi, 2009 ⁴⁶²	To evaluate the impact of oxybutynin transdermal system (OXY-TDS) and subsequent treatment on productivity among working participants	2878 and 1112 were employed (that formed the study population)	92.2	53.51%	OXY-TDS 3.9mg/day, twice weekly patch applications	6 months	MATRIX study: Community - based; 2978 adults aged ≥18 years with symptoms of OAB	Participants experienced significant improvements in mean scores for all four WPQ (Work Productivity Questionnaire) scales (p<=0.0002) and the mean WPQ Index decreased from 8.2 to 5.5 (p<0.0001). The WPLS (Work Productivity Loss Score) decreased from 7.7% to 5.2% (p<0.0001)
Oxybutynin MATRIX study	Newman, 2008 ⁴⁶³	To evaluate the effectiveness of transdermal oxybutynin (OXY-TDS) in improving HRQoL in a community - based adult population	2878	87.2	NR	OXY-TDS 3.9mg/day, twice weekly patch applications	6 months	MATRIX study: community - based; men and women aged ≥18 years having at least one symptom of OAB, such as urge UI, urgency, and/or frequency	Among all participants, 16.5% discontinued OXY-TDS due to adverse events. Overall, this study found that OXY-TDS administered resulted in improvement in HRQoL, with the medication having its greatest effect on the impact of incontinence, severity of symptoms, and role limitations

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Darifenacin	Zinner, 2008 ⁴¹³	To investigate patient -reported outcomes and clinical parameters during darifenacin treatment in OAB patients who expressed dissatisfaction with prior extended - release oxybutynin or tolterodine therapy	497	84.1	82.9	7.5mg darifenacin once daily with the possibility of up-titrating to 15mg after 2 weeks, for up to 12 weeks	12 weeks	Men and women (≥18 years of age) with OAB symptoms [an average of ≥8 micturitions/24 hours and ≥1 urgency episode/24 hours, with or without urgency urinary incontinence episodes] for at least 6 months prior to randomization, and with a baseline score of ≥2 on the Patient Perception of Bladder Condition questionnaire at screening. Patients were required to be naive to darifenacin treatment, to have received at least 1 week of treatment with oxybutynin ER or tolterodine ER within the year prior to this trial and to report that they were dissatisfied with	Darifenacin treatment resulted in statistically significant improvements in PPBC scores, micturition frequency, urgency and UUI episodes from baseline at 12 weeks. More than 85% of patients expressed satisfaction with darifenacin. The odds (and 95% CI) for improvement in PPBC amongst previous recipients of oxybutynin ER or tolterodine ER were 2.08 (1.48, 2.92) and 1.77(1.29, 2.43). The odds for reporting satisfaction (and 95%CI) were 4.35 (2.90, 6.53) amongst previous oxybutynin ER recipients and 5.23 (3.50, 7.80) for tolterodine ER recipients, representing an odd ratio (95% CI) of 0.83 (0.50, 1.40). 14.2 % discontinued in group who had prior treatment with oxybutynin and 10.4 % in group who had prior treatment with tolterodine. 58.4% had AEs, 20.1% dry mouth,

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
								the most recent of these treatments	14.1% constipation, 6.6% urinary tract infection, 3.6% headache, 3.2% nausea, 2.6% dyspepsia, 2.2% dry eye, and 2% upper respiratory tract infection. 40.1% of total patients reported ≥90% improvement in number of UUI episodes/week, 39.1% of patients in group that had prior treatment with oxybutynin reported ≥90% improvement, and 40.4% in group that had prior treatment with tolterodine reported ≥90% improvement.

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Fesoterodine	Wyndaele, 2009 ⁴⁶⁴	To evaluate the efficacy and tolerability of flexible -dose fesoterodine in subjects with overactive bladder who were dissatisfied with previous tolterodine treatment	516	77	50	Fesoterodine 4mg once daily for 4 weeks; thereafter, daily dosage maintained at 4mg or increased to 8mg	12 weeks	Men and women aged ≥18 years with self-reported OAB symptoms for ≥3 months with a mean micturition frequency of ≥8 micturitions per 24 hours and mean number of urgency episodes ≥3 per 24 hours in a 5-day bladder diary; they had to rate their bladder condition as causing at least 'some moderate problems' on the PPBC questionnaire at baseline; they were required to have been treated with tolterodine or tolterodine ER for OAB within 2 years of screening	Approximately 80% of subjects who responded to the TSQ (Treatment Satisfaction Question) at week 12 reported satisfaction with treatment; 38% reported being very satisfied. 8.5% of patients reported no problems on the PPBC scale; 38.9% patients reported 'Usually able to finish what I am doing' on the UPS (Urgency Perception Scale) scale. Significant improvements from baseline (p<0.0001) exceeding the minimally important difference (10 points) were observed in OAB-q Symptom Bother and Health-Related Quality of Life scales and all four HRQL domains.

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Botulinum-A toxin	Werner, 2005 ⁴⁶⁵	To investigate the efficacy and safety of botulinum -A toxin treatment for non-neurologic detrusor overactivity incontinence	26	100	100	100 units of botulinum -A toxin(BTX-A) injected into the detrusor at 30 sites	One day	Women with urge incontinence and urodynamically demonstrable detrusor overactivity incontinence who failed to respond to various antimuscarinic	53.8% women were dry after 4 weeks, 65% after 12 weeks, and 60% after 36 weeks. 2 women failed to respond. 15.4% showed subjective improvement in effect on life and 11.5% showed subjective improvement in urge incontinence after 36 weeks. Within the 51 followup visits, 30.8% patients had 9 urinary tract infections

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Role of urodynamics in evaluation of outcomes	Malone-Lee, 2009 ³⁴⁵	The place of urodynamics in the evaluation of patients with symptoms of the overactive bladder by comparing the response to antimuscarinic therapy in those with and with no urodynamically verified symptoms	356			Oxybutynin 2.5 mg twice daily and bladder retraining	6-8 weeks	Women ≥18 years with symptoms of overactive bladder and urgency, with or without urgency incontinence	<p>Patients respond equally to antimuscarinic therapy independent of urodynamic results. Detrusor instability-no detrusor Change from baseline 0 (2-6) / 0 (2-6) Dry mouth 84% / 70% Constipation 32% / 22% Heartburn 27% / 23% Dry skin 18% / 5% Headache 10% / 3.5% Dry eyes / 5% / 1%</p> <p>4 were excluded 76% had detrusor instability on cystometry</p>
Adherence to antimuscarinic medication	Balkrishnan, 2006 ⁴⁶⁶	Relationship between adherence to antimuscarinic medication and health care services utilization.	275	76	100	Antimuscarinic medications; possessions score was calculated as the days of antimuscarinic prescriptions supply dispensed divided by the number of days between these prescription refills.	6 months or more	Enrollees in Medicare magnet care plan in the southern US, 16-24% men; 73-74 years old who dispensed antimuscarinic drugs every 6 months	Charlson index comorbidity, patient perception of quality of life, and total number of prescribed medications during the year before enrollment in Medicare where predictors of poor adherence to antimuscarinic drugs.

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Adherence to antimuscarinic medication	Yu, 2005 ⁴⁶⁷	Predictors of adherence to medications for over active bladder syndrome	2,496	80		Tolterodine, Oxybutynin, Oxybutynin ER	6-12 months	20% random sample of California Medicaid program 20-25% men, 63-64 years old who dispersed any OAB/UI medication	Discontinuation-16% Hazard ratios of drug persistence White race -insignificant Tolterodine vs. Oxybutynin 0.7(0.67; 0.81) Previous antipsychotics use 0.85; 0.83; 0.88) Hazard ratios of drug adherence; Tolterodine vs. Oxybutynin 1.75 (1.10; 2.78) Oxybutynin ER vs. Oxybutynin 2.25 (1.36; 3.75)

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Cost effectiveness	Perfetto, 2005 ⁴⁶⁸	1-year total healthcare costs for patients with overactive bladder	Simulation model			Tolterodine tartrate extended release capsules (tolterodine ER) versus extended release oxybutynin chloride (oxybutynin ER).			Tolterodine ER had lower monthly drug and medical management costs
Cost effectiveness	Hughes, 2004 ⁴⁶⁹	Cost-Effectiveness Analysis of Extended-Release Formulations of Oxybutynin and Tolterodine for the Management of Urge Incontinence	Simulation study			Oxy-IR 5mg tablets Oxy-XL 10mg tablets Tol-IR 2mg tablets Tol-ER 4mg tablets			The incremental cost per incontinent-free week for Oxy-IR (versus no treatment) ranged from £2.58 to £16.59. Oxy-XL and Tol-ER were more effective than Oxy-IR but at additional costs per incontinent-free week. Tol-IR did not appear to be a cost-effective option as it was less effective and more costly than the extended-release formulations
Cost effectiveness	O'Brien, 2001 ⁴⁷⁰	Cost-effectiveness of Tolterodine for Patients with urge incontinence who discontinue initial therapy with Oxybutynin	Simulation study with Markov model			Tolterodine in patients who discontinued Oxybutynin			The incremental cost per QALY was Can \$9982 and appeared to be robust

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Cost effectiveness	Varadharajan, 2005 ⁴⁷¹	Post treatment medical costs for patients with overactive bladder				Oxybutynin chloride immediate release (oxybutynin IR), oxybutynin chloride extended release (oxybutynin ER), or tolterodine extended-release tartrate capsules (tolterodine ER).			Costs for patients taking oxybutynin IR were 48% higher than costs for patients taking tolterodine ER (P = .026), and costs for patients taking oxybutynin ER were 191% higher than costs for patients taking tolterodine ER (P <.0001).
Cost effectiveness	Ko, 2006 ⁴⁷²	The cost-effectiveness of various antimuscarinic agents for the treatment of overactive bladder	Decision-analysis model			Darifenacin, solifenacin, trospium, immediate release oxybutynin, extended-release oxybutynin, transdermal oxybutynin, immediate-release tolterodine, and extended-release tolterodine			Expected costs for each patient with OAB ranged from \$3373 when treated with solifenacin to \$3769 when treated with immediate-release oxybutynin. The average cost/patient with continued and successful treatment was lowest for solifenacin (\$6863). Solifenacin dominated all other antimuscarinic agents because they were associated with high costs and low effectiveness.

Appendix Table F33. Clinical outcomes after pharmacological treatments in nonrandomized studies (continued)

Treatment	Reference	Aim	Number	% Women	% with UI	Treatment	Duration	Population	Results
Cost effectiveness	Yu, 2005 ⁴⁶⁷	Cost effectiveness of antimuscarinic medications	2,496	80	Not reported	Tolterodine Oxybutynin extended-release Oxybutynin Other OAB drugs	6 months- 12 months	20% random sample of the administrative files provided by the California Medicaid program (Medi-Cal) from January 1999 to April 2002 with chronic OAB/UI	Expected costs for each patient with OAB ranged from \$3373 when treated with solifenacin to \$3769 when treated with immediate-release oxybutynin. The average cost/patient with continued and successful treatment was lowest for solifenacin (\$6863). Solifenacin